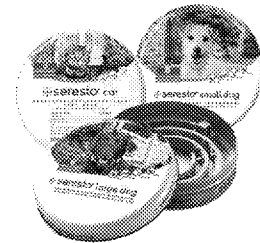


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# Review of Seresto Pet Collar Incidents Data

Presentation for Bayer  
June 9<sup>th</sup>, 2016



U.S. Environmental Protection Agency  
Office of Pesticide Programs  
Health Effects Division (HED)

# Seresto Overview

- Seresto: pet collar (dog & cat) containing 4.5% flumethrin and 10.0% imidacloprid
  - Intended to provide 8 months of control for fleas and ticks
- Submitted on September 23, 2010 as part of a new AI; Non-Food; Indoor Use submission for flumethrin
  - Seresto (EPA Reg. No. 11556-155) is currently the only registered end-use product for flumethrin
- Registered on March 16, 2012
- Currently Pending Registration with PMRA
  - Working closely with PMRA on analysis
  - Reviewed PMRA's Plausibility Analysis
  - Will review PMRA's Causality Analysis
- In Europe there are 4 Seresto collars authorized: one for cats, one for cats and dogs, one for small dogs (<8kg), and one for large dogs (>8kg).

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## Seresto Incident Review

- OPP review of pet incidents by product in IDS query
- HED reviewed Seresto collar incident data using 4 levels:
  1. Incident counts reported to Aggregate IDS
  2. Reporting Odds Ratio (ROR)
  3. Incident Rate Ratio (IRR)
  4. Additional analyses, by VedDRA code symptom
- Additionally, HED reviewed the most recent Bayer quarterly data for seasonal trends

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The query in the above was Jan 1, 2012- July 29 2015. This graph is included merely to illustrate why OPP got worried about Seresto

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## Level 1. IDS Aggregate Query Results

from CY 2013 – 2014

- In terms of incident counts, Seresto ranked #1 , for death + major incident counts in IDS among Bayer products;

EPA Registration Number	Death	Major	Moderate/Minor/ No Effect	Total
11556-155 (Seresto)	190	627	8709	9526
11556-144,143,142,141 (K-9 Advantix II)	223	513	11303	12039
11556-152,151 (Advantage II cats)	112	242	3907	4261
11556-127,130,128,125 Advantage plus dogs	86	187	2003	2276
11556-134,135 K9 Advantix	38	5	141	184

### Limitations:

- Pet incident reports are counts , by severity
  - species unknown
- Not normalized
- No descriptive detail available

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Top three products  
Seresto  
Frontline plus for dogs  
Frontline plus for cats

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## Level 2. Reporting Odds Ratio

- Reporting Odds Ratio (ROR) calculated for all pet Spot On products with ten or more deaths reported in IDS
- ROR measures the odds of fatal or high severity incidents for Seresto compared to the odds of fatal or high severity incidents for all other products
- Calculation:
  1.  $X = \text{death} + \text{major incident reports for Product A} / \text{all other (less severe) incident reports for Product A}$
  2.  $Y = \text{death} + \text{major incident reports for all other (not Product A) products} / \text{all other (not Product A) less severe incident reports}$
  3.  $ROR = X/Y$

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## Level 2. Reporting Odds Ratio

### Benefits and Limitations

- **Does not require sales data**
- Incident data – issues with using counts:
  - Pet product labeling is inconsistent
    - Seresto = 1 registration # for all species/sizes combined
    - Other products have multiple registration #s by species, animal size
  - Hence, IDS reports, which are organized by product registration #, do not reflect these important distinctions

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combined the following:

• Advantage II for cats (11556-150 – kitten, 1156-151 – small cat, 11556-152 – large cat), □ Advantage II for dogs (11556-128 – small dog, 11556-125 – medium dog, 11556-127 – large dog, and 11556-130 – extra-large dog) □ K9 Advantix II (11556-132 –small dog, 11556-133 medium dog, 11556-134 extra-large dog, 11556-135 large dog)

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# Reporting Odds Ratio

ROR Results for **Deaths Only** – Bayer product comparison

EPA Registration Number	Death	Total	ROR	95% Confidence Interval
11556-155 (Seresto)	190	9526	0.81	(0.68, 0.96)
11556-144,143,142,141 (K-9 Advantix II)	223	12039	0.70	(0.60, 0.83)
11556-152,151 (Advantage II cats)	112	4261	1.18	(0.96, 1.45)
(11556-127,130,128,125) Advantage plus dogs	86	2276	1.77	(1.41, 2.24)
(11556-134,135) (9 Advantix	38	184	11.71	(8.12,16.88)

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We calculated ROR for all pet products with 10 or more deaths- this table is the top three products in terms of pet deaths + major

IDS data from 2013/2014 was originally used \*\*\*These ROR have been updated with more recent data\*\*\*

K9 product only includes large dog

Frontline for dogs

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# Reporting Odds Ratio

ROR Results for **Deaths + Major Incidence** – Bayer product comparison

EPA Registration Number and Product Name	Death + Major Incidence	Total	ROR	95% Confidence Interval
11556-155 (Seresto)	817	9526	1.16	(1.06, 1.27)
11556-144,143,142,141 (K-9 Advantix II)	736	12039	0.65	(0.59, 0.71)
11556-152,151 (Advantage II cats)	354	4261	1.07	(0.95, 1.21)
(11556-127,130,128,125) Advantage plus dogs	273	2276	1.68	(1.47, 1.92)
(11556-134,135) K9 Advantix	43	184	3.63	(2.57, 5.12)

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We calculated ROR for all pet products with 10 or more deaths- this table is the top three products in terms of pet deaths + major

IDS data from 2013/2014 was originally used \*\*\*These ROR have been updated with more recent data\*\*\*

K9 product only includes large dog

Frontline for dogs

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## Level 3. Incident Rate Ratio (IRR)

- Seresto and other Bayer product sales data was obtained
- This allowed HED to:
  - Calculate the Incident Rate Ratio
    - a standard method of comparing incident rates
  - Control for 8 months Seresto vs. 1 month Spot-On
    - $IR_A$  = incident counts for Product A/ "pet-months"\* for Product A
    - $IR_B$  = incident counts for Product B/ "pet-months" for Product B
    - $IRR = IR_A / IR_B$
- Used the Poisson Regression Model (with "offset")
  - Allows one to obtain confidence limits around IRR
  - Can determine statistically significant differences between products

\*Pet-months = sales x control period

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Seresto last 8 months = 8,000 pet months of exposure whereas Spot-ons = 1,000 pet months of exposure

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## Level 3. Incident Rate Ratio

Table: IRR comparison between Seresto and K9 Advantix II

Year	Outcome	Comparison	IRR (95% C.I.)
2013+2014	Death + major	Seresto vs. K9 Advantix II Dog	3.10 (2.80, 3.42)
	Total Incidents	Seresto vs. K9 Advantix II Dog	2.21 (2.15, 2.27)
NOTE: HED did not have annual sales data for K9 Advantix II (HED had cumulative sales for 4 years (2011-2014) for K-9 Advantix II and derived approximate total 2013 and 2014 sales number by dividing the four year 2011-2014 total by 4 and then multiply by 2)			

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Outcome Death  
Seresto vs. Frontline – 2014

IRR (95% C.I.) = 16.55 (12.33 , 22.21)

Need to consider limitations in data- reporting high severity cases for symptoms lasting 60 days or more whereas other registrants may classify rash etc as moderate –

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## Level 3. Incident Rate Ratio

### Benefits:

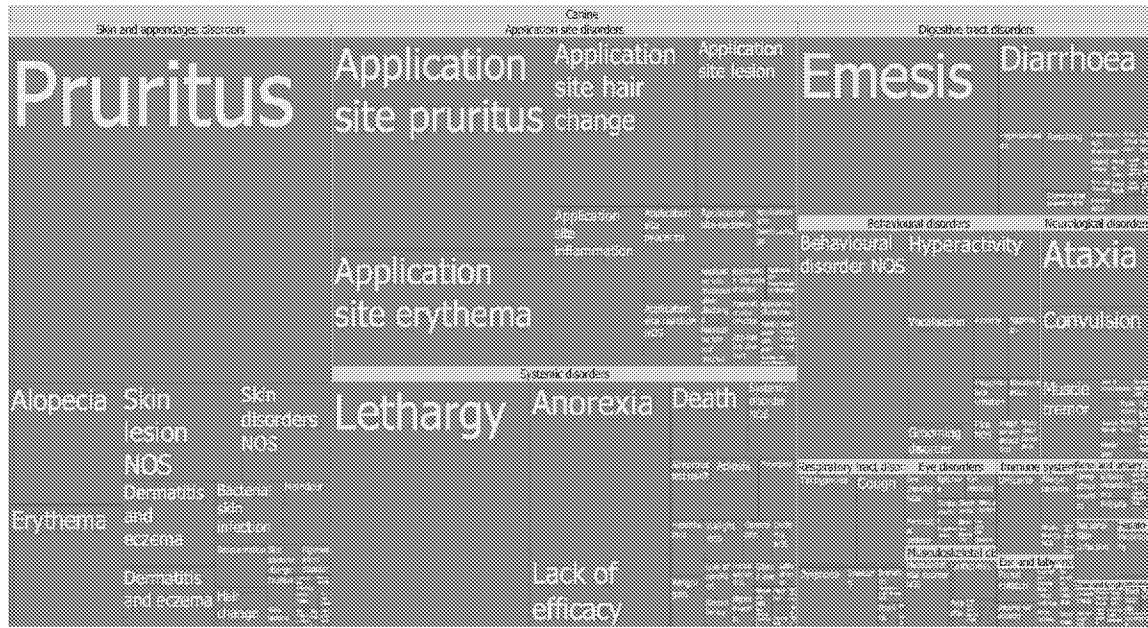
- The most valid method of analysis
- Sales data incorporated

### Limitations:

- Data inconsistencies
  - Seresto has one registration number for all collars
  - Sales data was approximated
    - Availability of sales information varied among products
  - Use of 2013/2014 data & the Weber Effect
  - Variability in reporting practices/categorizations by company –
    - But comparisons here only within Bayer

## Level 4 Tree Diagram- Canine

data signals- Seresto, by symptom (VedDRA coded)



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Multivariate tree diagram – check for signals

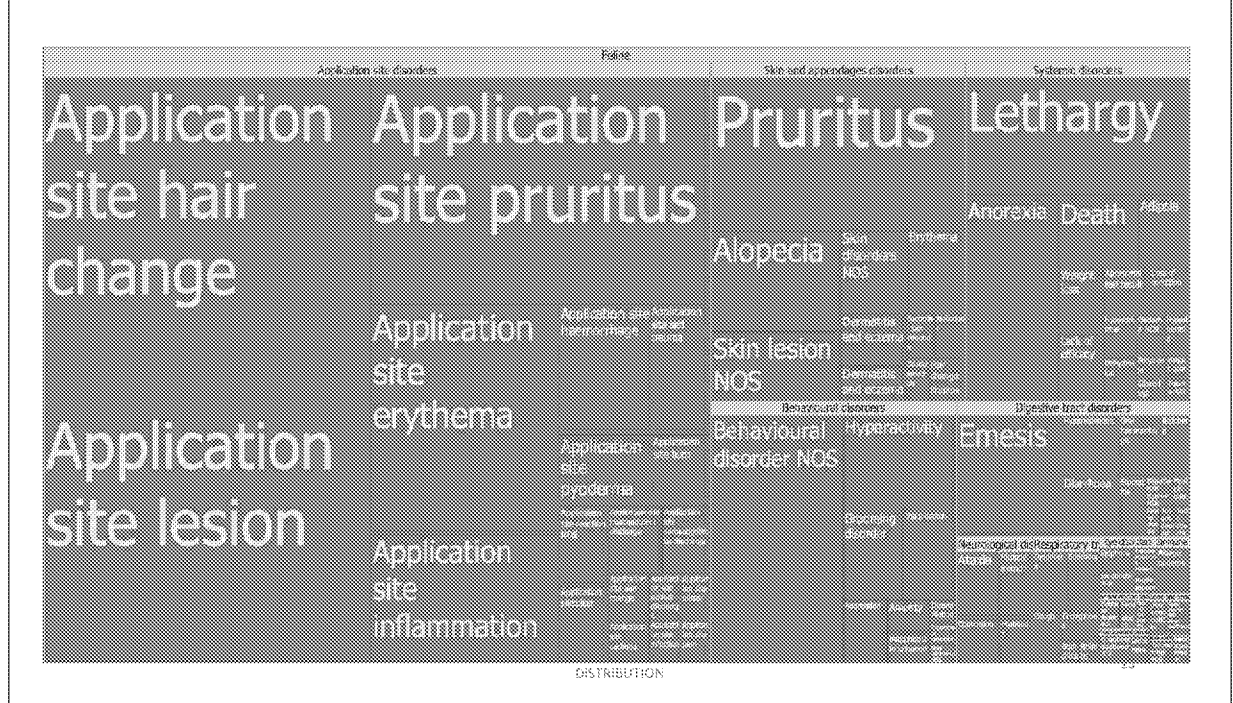
Seresto- 817= deaths + majors

GREEN BOXES DO NOT DIFFER FROM THE AVERAGE RISK

Each box represents # of death+ majors, the height represents the deaths, and color represents the Reporting Odds Ratio

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# Level 4 Tree Diagram -- Feline data signals- Seresto, by symptom (VedDRA coded)



Multivariate tree diagram – check for signals

Seresto- 817= deaths + majors

GREEN BOXES DO NOT DIFFER FROM THE AVERAGE RISK

Each box represents # of death+ majors, the height represents the deaths, and color represents the Reporting Odds Ratio

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## Recent Seresto Data Submission

- Third quarter 2015 Bayer incident data was received in October 2015.
- OPP noted a jump in death and major severity incidents for Q3
  - Increase from 185 incidents to 343 incidents
- HED compared Seresto and three other Bayer pet products using incident counts for the 6 most recent quarters of data
- Based on newest available incident data
- Looking for a similar jump in incidents among other pet products that would indicate a seasonal trend

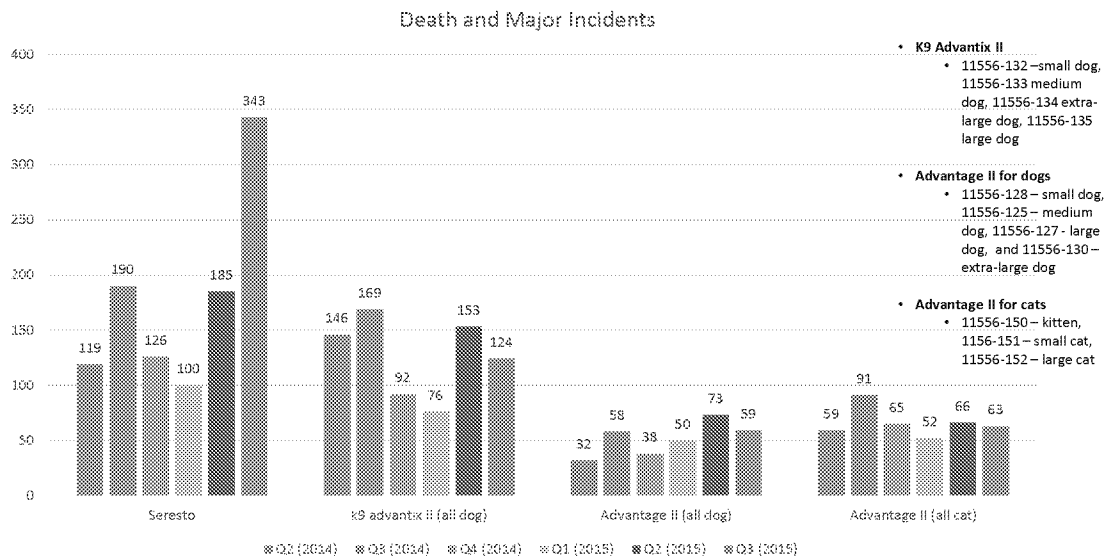
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In Mid-October , When Bayer submitted the 3rd quarter Seresto incidents there was an increase in deaths and majors. We compared the same 6 quarter for 4 bayer products to see if other products followed this trend or if it was just Seresto.

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Figure 1. Bayer **Death and Major** Domestic Animal Incidents Reported to Aggregate IDS for 2014 Q2,Q3,Q4 and 2015 Q1, Q2, and Q3



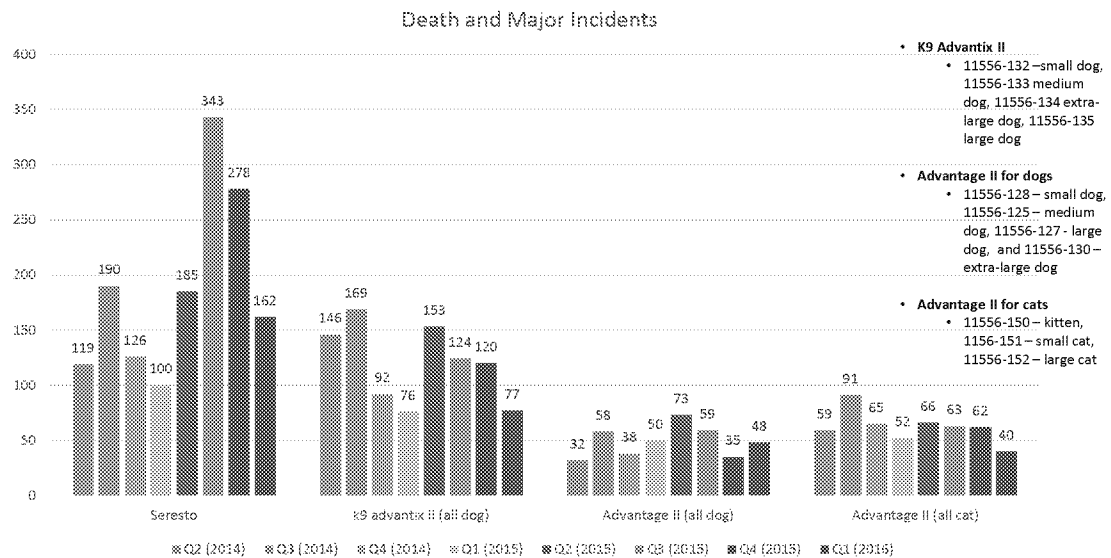
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What happened? Is this normal? Well- the other products did not double from Q2 to Q3

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Figure 2. Bayer **Death and Major** Domestic Animal Incidents Reported to Aggregate IDS for 2014 Q2,Q3,Q4 and 2015 Q1,Q2,Q3,Q4 and 2016 Q1



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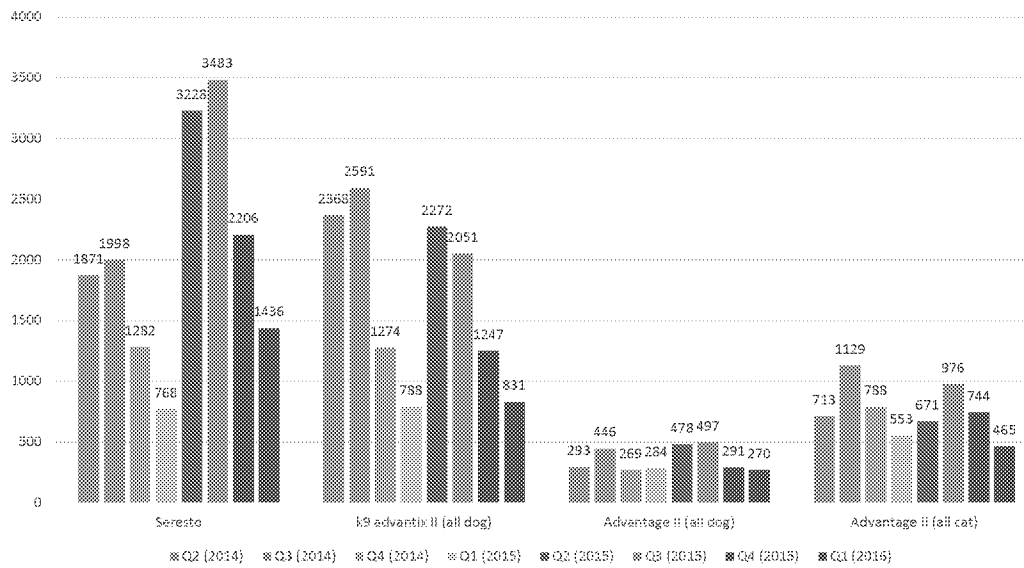
16

What happened? Is this normal? Well- the other products did not double from Q2 to Q3

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Figure 3. Bayer Domestic Animal **Total Incidents** Reported to Aggregate IDS for 2014 Q2,Q3,Q4 and 2015 Q1,Q2,Q3, Q4 and 2016 Q1



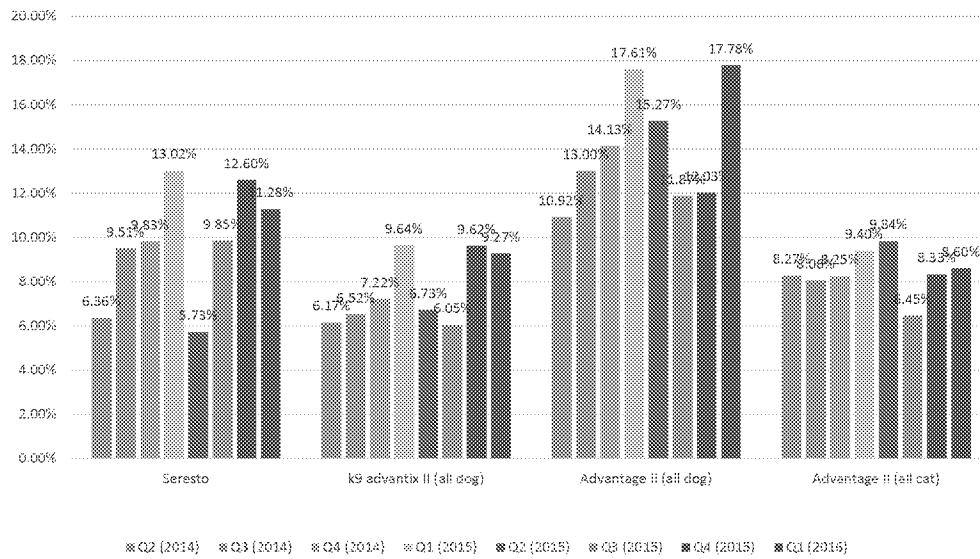
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Combines all species and sizes for the non-Seresto Bayer products- paste in the product combo list!!

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Figure 4. Percentage of Death and Major Severity Incidents Compared to Total Incidents, by Product



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## Acute Toxicity Review

- Based on slow release of active ingredients, waivers were granted for oral tox, dermal tox, inhalation tox and eye irritation
- Not a dermal sensitizer
- Category IV for primary dermal irritation

## Companion Animal Safety Review

- Protocols were submitted and accepted prior to conducting studies
- A total of 8 companion animal safety studies were submitted
- Studies classified as acceptable; support the proposed use of Seresto on adult dogs and puppies 7 weeks of age and older, and adult cats and kittens 10 weeks of age and older

## Efficacy Review

- A total of 20 studies were submitted
- Claim supported: “For 8 month prevention and treatment of ticks, fleas on dogs and cats”

## Timeline of Initial Bayer Communications

- 7/27/15: EPA received a press inquiry re: Seresto  
“Is EPA aware of any incidents surrounding Seresto and are there any ongoing investigations?”
- 7/29/15; first call with Bayer
  - Objective of call was to ask if they are aware of a high number of reported incidents
- 7/30/15; second call with Bayer
  - Objective of call was to request submission of incident data
- 7/30/15; Bayer emails sample of enhanced reporting format
- 8/3/15; Bayer emails incident information that was originally submitted to PMRA and published information regarding “Weber Effect”
  - Format Issues

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## Call with Bayer on 2015 Q3 incident data

- EPA- Why the jump in FY 15 Q3 major incidents?

### Bayer Response:

- Large increase in collar sales in FY 15 Q2
  - Q3 incidents likely reflective of Q2 sales
  - Sales substantially above that of the previous quarter
- Bayer is conservative with high severity coding; 60% are moderate
  - >60 days dermal rash is classified as DB (major severity)
  - Unclear how other registrants are coding

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DA – Death – if the domestic animal died or was euthanized;

DB – Major – if the domestic animal exhibited or was alleged to have exhibited symptoms which may have been life-threatening or resulted in residual disability;

DC – Moderate – if the domestic animal exhibited or was alleged to have exhibited symptoms which are more pronounced, more prolonged or of a more systemic nature than minor symptoms and included some treatment and return to pre-exposure state;

DD – Minor – if the domestic animal was alleged to have exhibited symptoms, but they were minimally bothersome and resolved rapidly;

DE – Unknown – if symptoms are unknown or not specified.

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## Limitations with Pet Product Incident Data

Potential confounders described by Bayer:

- Variability between companies
  - Bayer has a 24 hour reporting hotline
  - Differences among registrants regarding severity classification
- Variability between products
  - Weber effect
  - Seeing the collar each day serves to visually remind pet owners of the exposure
  - Seresto has one registration # for all species/sizes whereas other products can have a separate registration # for the species/sizes
- Is variability still an issue?
  - No issue of variability between companies if Seresto vs. Bayer's products
  - Weber effect should not be a concern for the data in recent years

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Advantage II for cats (11556-150 – kitten, 1156-151 – small cat, 11556-152 – large cat), □Advantage II for dogs (11556-128 – small dog, 11556-125 – medium dog, 11556-127 - large dog, and 11556-130 – extra-large dog)□K9 Advantix II (11556-132 –small dog, 11556-133 medium dog, 11556-134 extra-large dog, 11556-135 large dog)

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